REMARKS

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

I. Restriction requirement and unity of invention

Claims directed to methods of using the polynucleotides for detecting polynucleotides by hybridization and/or PCR (i.e., Claims 34-36), for assessing toxicity of a test compound (i.e., Claim 44), and for screening for effectiveness in altering expression (i.e., Claim 43), could and should be examined together with the product claims from which they depend, per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants presume that these method claims will be rejoined, upon determining allowability of the product claims from which they depend.

In addition, Applicants request withdrawal of the holding of lack of unity of invention between claims drawn to polynucleotides and claims drawn to the polypeptides encoded by the polynucleotides (i.e. Claims 21-23 and 37-42).

The Patent Office asserts that "[t]he polynucleotide of claim 33, which is drawn to an isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 32, encompasses polynucleotides that, when expressed, result in the production of proteins that do *not* correspond to the polypeptide of claims 21-23. Therefore, the polynucleotide of Group XXXVIII, particularly the polynucleotide of claim 33, does not share a corresponding special technical feature with the polypeptide of claims 21-23, and thus the inventions do not have unity of invention". (Office Action, October 9, 2003; page 4).

Applicants do not agree with the Patent Office position. Nevertheless, to expedite prosecution of the subject application, the "fragment" language has been deleted from Claim 21. Applicants respectfully submit that in light of the claims currently amended in this paper, unity of invention clearly does exist between claims drawn to polynucleotides (i.e. Claims 24-30, 32-36, and 43-45) and claims

drawn to the polypeptides encoded by the polynucleotides (i.e. Claims 21-23 and 37-42).

II. Objections to the Specification

On page 9 of the Office Action, it was noted that the filing dates if certain provisional applications listed in the priority claim do not correspond to the filing dates listed in the Declaration filed on October 1, 2001. In fact, the dates listed in the priority claim of the Specification as amended on July 16, 2003 is correct. If the Examiner feels it is necessary, a substitute Declaration can be obtained.

III. Claim Objections

A substitute Sequence Listing is filed herewith, which corrects the numbering of the various polypeptide and polynucleotide sequences. As amended, the claims recite the elected subject matter.

IV. Indefinitness rejections under 35 U.S.C. § 112, second paragraph

Claim 21 has been amended by deleting the recitation of a "biologically active fragment". Claim 32 has been amended to recite a the polynucleotide that is "fully complementary". By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include polynucleotides encoding biologically active fragments of SEQ ID NO:7. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

Furthermore, Applicants have amended and are submitting a substitute sequence listing as well re-numbered Tables 1-4 to reflect that the polynucleotide of SEQ ID NO:37 encodes the polypeptide of SEQ ID NO:7.

While not conceding to the Patent Office position, it is believed that Claims 24 and 32, as amended, recite patentable subject matter. Therefore, withdrawal of this rejections is requested.

V. Utility rejection under 35 U.S.C. § 101 and § 112, first paragraph

Claims 24-30, 32-33, and 45 stand rejected under 35 U.S.C. § 101 based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that:

- "...further experimentation is required to establish a "real world" use for the polynucleotide of SEQ ID NO:37. This type of utility is not conisdered a "substantial utility". (Office Action,

October 9, 2003; page 12-13).

- "...the claimed polynucleotide has no specific and substantial utility". (Office Action, October 9, 2003, page 14).

The rejection of claims 24-30, 32-33, and 45 **is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.**

The invention at issue is a polynucleotide corresponding to a phophatidyl inositol 3- kinase that is expressed in reproductive, nervous, gastrointestinal, hematopoietic, and cardiovascular tissues in humans. The claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions.

Applicants submit with this paper two expert Declarations under 37 C.F.R. § 1.132, with respective attachments, and ten (10) scientific references filed before or shortly after the July 28, 1998 priority date of the instant application. The Rockett Declaration and the Iyer Declaration, and the ten (10) references fully establish that, prior to the July 28, 1999 filing date of the parent application, it was well-established in the art that:

> polynucleotides derived from nucleic acids expressed in one or more tissues and/or cell types can be used as hybridization probes -- that is, as tools -- to survey for and to measure the presence, the absence, and the amount of expression of their cognate gene;
>
> with sufficient length, at sufficient hybridization stringency, and with sufficient wash stringency -- conditions that can be routinely established -- expressed polynucleotides, used as probes, generate a signal that is specific to the cognate gene, that is, produce a gene-specific expression signal;
>
> expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts, in toxicology, particularly toxicology studies conducted early in drug development efforts, and in phenotypic characterization and categorization of cell types, including neoplastic cell types;
>
> each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically

more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

nucleic acid microarrays increase the parallelism of expression measurements, providing expression data analogous to that provided by older, lower throughput techniques, but at substantially increased throughput;

accordingly, when expression profiling is performed using microarrays, each additional gene-specific probe that is included as a signaling component on this analytical device increases the detection range, and thus versatility, of this research tool;

biologists, such as toxicologists, recognize the increased utility of such improved tools, and thus want a gene-specific probe to each newly identified expressed gene to be included in such an analytical device;

the industrial suppliers of microarrays recognize the increased utility of such improved tools to their customers, and thus strive to improve salability of their microarrays by adding each newly identified expressed gene to the microarrays they sell;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

failure of a probe to detect changes in expression of its cognate gene does not diminish the usefulness of the probe as a research tool; and

failure of a probe completely to detect its cognate transcript in any single expression analysis experiment does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function, or the biological function of the polypeptide it encodes. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Rockett Declaration and the Iyer Declaration the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise biological function.

VI. Enablement rejections under 35 U.S.C. § 112, first paragraph

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility (Office Action, October 9, 2003, page 18). To the extent that the rejection under § 112, first paragraph, is based on improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

In addition, Claims 24, 26, 28-30, 32-33, and 45 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed variants and fragments. In particular, the Office Action asserts that "undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention". (Office Action, October 9, 2003; page 19).

Claim 21 has been amended by deleting the "variant" and "fragment" language. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include polynucleotides encoding biologically active fragments, immunogenic fragments, and variants of SEQ ID NO:7. Applicants do not concede to the Patent Office position; Applicants are amending the claim solely to obtain expeditious allowance of the instant application.

VII. Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 24, 26, 28-30, 32-33, and 45 were rejected under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. The Office Action asserts that "[t]he claim(s) contain subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention". (Office Action, October 9, 2003; pages 15-16). This rejection is traversed.

Claim 21 has been amended by deleting the "variant" and "fragment" language. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include polynucleotides encoding biologically active fragments, immunogenic fragments, and variants of SEQ ID NO:7. Applicants do not concede to the Patent Office position; Applicants are amending the claim solely to obtain expeditious allowance of the instant application.

VIII. Rejection under 35 U.S.C. §§ 102(a) and 102(b)

Claims 24 and 33 were rejected under 35 U.S.C. § 102(a) because they are allegedly anticipated by Skolnik et al. (*Cell* 65:83-90). In particular, the Office states that Claim 24 "is drawn to an isolated polynucleotide encoding a biologically active fragment of SEQ ID NO:7 and an immuogenic fragment of SEQ ID NO:7". (Office Action, October 9, 2003, page 24). As aforementioned, Applicants submit that Claim 21 has been amended by deleting the recitation of a "biologically active fragment" and "an immunogenic fragment." Therefore, withdrawal of the rejection of Claims 24 and 33 based on 35 U.S.C. § 102(a) is respectfully requested.

Claims 24 and 26 were rejected under 35 U.S.C. § 102(b) because they are allegedly anticipated by Inukai et al. (*J. Biol. Chem.* 271:5317-5320). In particular, the Office states that Claim 24 "is drawn to an isolated polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:7, a biological fragments of SEQ ID NO:7, and an immunogenic fragment of SEQ ID NO:7". Claim 26 "is drawn to an isolated polynucleotide

encoding a poplypeptide comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:7". (Office Action, October 9, 2003, page 24-25).

To expedite prosecution of the subject application, the "variant" and "fragment" language has been deleted from the claims. Applicants expressly do not disclaim equivalents of the claimed subject matter.

For at least the above reasons, Applicants respectfully request that the Examiner withdraw the rejection over Inukai.

Claim 33 was rejected under 35 U.S.C. § 102(b) as being anticipated by GenBank Accession Number M61906 (gi: 189424). In particular, the Office states that Claim 33 "is drawn to an isolated polynucleotide comprising at least 60 nucleotides of a polynucleotide of Claim 32. GenBank Number M61906 discloses the sequence of a nucleic acid that is at least 60 nucleotides of a polynucleotide of Claim 32". (Office Action, October 9, 2003, page 25).

To expedite prosecution of the subject application, Claim 33 has been cancelled. Applicants expressly do not disclaim equivalents of the claimed subject matter.

IX. Rejections under 35 U.S.C. § 103(a)

Claims 28-30 were rejected under 35 U.S.C. § 103(a) because the claimed recombinant polynucleotides, cells, and methods of producing polypeptides are allegedly obvious over Inukai et al. (GenBank Accession Number D64048) or Skolnik et al. This rejection is traversed.

As discussed above in § VIII, Claim 24 does not encompass polynucleotides which are disoclosed or suggested by either the Inukai et al. or Skolnik et al. references. Therefore, Inukai et al. and Skolnik et al. cannot be used as references against the claimed subject matter, and the Patent Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103. For at least these reasons, withdrawal of these rejections is requested.

Please charge Deposit Account No. **09-0108** in the amount of **$110.00** as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. 09-0108.

Respectfully submitted,

INCYTE CORPORATION

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TABLE 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	31	132240	BMARNOT02	132240H1 and 132240R1 (BMARNOT02), 3254142H1 (OVARTUN01), 1453821X14F1 and 1453821F6 (PENITUT01)
2	32	2180116	SININOT01	2180116H1 and 2180116T6 (SININOT01), 3046645H1 (HEAANOT01), 1918183H1 (PROSNOT06), and 1482405F1 (CORPNOT02)
3	33	2197671	SPLNFET02	2197671H1 (SPLNFET02), 666366X22R1 (SCORNOT01), 693783X14 (SYNORAT03), 824265X33F1 (PROSNOT06), 039482R1 and 039482F1 (HUVENOB01), 1453984T6 (PENITUT01), 1663987H1 (BRSTNOT09), and 125901R1 (LUNGNOT01)
4	34	2594943	OVARTUT02	2594943H1 (OVARTUT02), 3617557H1 (EPIPNOT01), 2269005R6 (UTRSNOT02), 1307764F6 (COLNFET02), 1377794F6 (LUNGNOT10), and 1286608H1 (BRAINOT11)
5	35	1513871	PANCTUT01	754239R6 (BRAITUT02), 1513871H1 (PANCTUT01), 2414420F6 (HNT3AZT01), 3291775F6 (BONRFET01), 3821451F6 (BONSTUT01)
6	36	156108	THP1PLB02	156108F1 and 156108H1 (THP1PLB02), 336346R6 (EOSIHET02), 1319528F1 (BLADNOT04), 2375549F6 (ISLTNOT01), SBFA04563F1, SBFA04977F1
7	37	2883243	UTRSTUT05	1342082F6 (COLNTUT03), 1933387T6 (COLNNOT16), 2766460F6 (BRSTNOT12), 2883243H1 (UTRSTUT05), 3524262H1 (ESOGTUN01), 3766487F6 (BRSTNOT24)

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
8	38	3173355	UTRSTUT04	1300803F6 and 1300803T6 (BRSTNOT07), 2477542F6 (SMCANOT01), 2477542T6 (SMCANOT01), 2875968H1 (THYRNOT10), 3173355F6 and 3173355H1 (UTRSTUT04), 3290825H1 (BONRFET01), 5192561H1 (OVARDIT06)
9	39	5116906	SMCBUNT01	267517F1 (HNT2NOT01), 263823R1 (HNT2AGT01), 5116906H1 (SMCBUNT01)
10	40	940589	ADRENOT03	029801R6 (SPLNFET01), 940589H1 (ADRENOT03), 1737403T6 (COLNNOT22), 1805477F6 and 1805477T6 (SINTNOT13), 2447613H1 (THP1NOT03), 3408563H1 (PROSTUS08), 3519506H1 (LUNGNON03), 3637343T6 (LUNGNOT30)
11	41	304421	TESTNOT04	304421H1, 304421X318B2, and 304421X323B2 (TESTNOT04), 2639579F6 (BONTNOT01), 2951859H1 (KIDNFET01)
12	42	1213802	BRSTTUT01	894574R1 (BRSTNOT05), 1213802H1 (BRSTTUT01), 1233414F1 and 1234238H1 (LUNGFET03), 1255782F2 and 1255782T1 (MENITUT03), 1455429F1 (COLNFET02), 1576102T1 (LNODNOT03), 2189267F6 (PROSNOT26), 2748179F6 (LUNGTUT11), 2831667H1 (TLYMNOT03), 3031229H1 (TLYMNOT05), 3054893H1 (LNODNOT08), 3797030F6 (SPLNNOT12), 3880154H1 (SPLNNOT11), 4852525H1 (TESTNOT10), 5514137H1 (BRADDIR01), 5518378H1 (LIVRDIR01)
13	43	1378134	LUNGNOT10	1378134H1 and 1378134X11 (LUNGNOT10), 2205185F6 (SPLNFET02), 4959694H1 (TLYMNOT05), SAMA00107F1, SAMA00160F1, SAMA00020F1

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
14	44	1490070	UCMCL5T01	432218H1 (BRAVUNT02), 1490070H1 (UCMCL5T01), 1535394F1 (SPLNNOT04), 1616509F6 and 1616509T6 (BRAITUT12), 2490845H1 (EOSITXT01), 2723789F6 (LUNGTUT10), SAOA00263F1
15	45	1997814	BRSTTUT03	855350R1 (NGANNOT01), 875417R1 (LUNGAST01), 895096R1 (BRSTNOT05), 1271348F1 (TESTTUT02), 1331289F6 (PANCNOT07), 1359243F1 (LUNGNOT12), 1540824T1 (SINTTUT01), 1839828H1 (EOSITXT01), 1997814H1 (BRSTTUT03), 2170638F6 (ENDCNOT03), 3751363F6 (UTRSNOT18)
16	46	2299715	BRSTNOT05	637354R6 and 637354T6 (NEUTGMT01), 1852144F6 (LUNGFET03), 2172576F6 (ENDCNOT03), 2232449F6 (PROSNOT16), 2299715H1 (BRSTNOT05), 2509737X325D2 (CONUTUT01), 2606210F6 (LUNGTUT07), 2692024F6 (LUNGNOT23), 2805893F6 (BLADTUT08), 2986160H1 (CARGDIT01), 3085382H1 (HEAONOT03), 3136101F6 and 3136587H1 (SMCCNOT01), 4249977H1 (BRADDIR01)
17	47	209854	SPLNNOT02	209854H1 and 209854T6 (SPLNNOT02), 3152165R6 and 3152165T6 (ADRENON04)
18	48	1384286	BRAITUT08	676123R6 and 676123T6 (CRBLNOT01), 989218X11 and 989218X12 (LVENNOT03), 1384286H1 (BRAITUT08), 3099868H1 (PROSBPT03), 4693167H1 (BRAENOT02)
19	49	1512656	PANCTUT01	322847X5 (EOSIHET02), 1253795T6 (LUNGFET03), 1512656H1 (PANCTUT01), 1561686X303D1 (SPLNNOT04), 2212305H1 (SINTFET03), 2697679H1 (UTRSNOT12), 3205172H1 (PENCNOT03), 5313318H1 (KIDETXS02)

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
20	50	2098635	BRAITUT02	1268848T1, 1268848X301F1, and 2157157H1 (BRAINOT09), 2098635H1 and 2098635R6 (BRAITUT02), 2198819F6, 2198819X301D4, 2198819X303D1, 2198819X309B2, and 2198819X309D4 (SPLNFET02), 2784975H2 (BRSTNOT13), 3320340H1 (PROSBPT03)
21	51	2446646	THP1NOT03	000297R6 and 000297X61 (U937NOT01), 2446646H1 (THP1NOT03), 2557274F6 (THYMNOT03)
22	52	2764911	BRSTNOT12	678618T6 and 678618X14 (UTRSNOT02), 2304126R6 (BRSTNOT05), 2764911H1 (BRSTNOT12), 2834475F6 (TLYMNOT03), 2915803F6 (THYMFET03), 3035012F6 (TLYMNOT05), SAFC00027F1, SAFC00254F1, SAFC02376F1, SAFC01609F1
23	53	3013946	MUSCNOT07	673753H1 (CRBLNOT01), 989218X11 and 989218X14 (LVENNOT03), 2821720F6 (ADRETUT06), 3013946F6, 3013946H1, and 3013946T6 (MUSCNOT07), 4693167H1 (BRAENOT02)
24	54	067967	HUVESTB01	067967X92, 067966R1, and 067967H1 (HUVESTB01), SAIA02074F1, SAIA03254F1, SAIA03603F1, and SAIA02259F1
25	55	346275	THYMNOT02	346275H1 (THYMNOT02), 609792X12 (COLNNOT01), SAGA03543F1, SAGA02528F1, and SAGA00285F1
26	56	283746	CARDNOT01	283746H1 and 283746X10 (CARDNOT01), 4903108H1 (TLYMNOT08), 557918X15 (MPHGLPT02), and 2379045F6 (ISLTNOT01)
27	57	2696537	UTRSNOT12	2696537H1 (UTRSNOT12), 3173337F6 (UTRSTUT04), 082658X100 (HUVESTB01), and 603219T6 (BRSTTUT01)

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
28	58	619292	PGANNOT01	613165F1 (COLNTUT02), 619292H1 and 619292X13 (PGANNOT01)
29	59	2054049	BEPINOT01	1736355F6 (COLNNOT22), 2054049H1 (BEPINOT01), 2379092T6 (ISLTNOT01), 3127284T3 (LUNGTUT12), 3136377F6 (SMCCNOT01), SBMA00545F1, SBMA00827F1, SBMA02930F1, SBMA02853F1
30	60	2843910	DRGLNOT01	036294X71 (HUVENOB01), 066017X102, 068399R1, and 068399X3 (HUVESTB01), 1527276H1 (UCMCL5T01), 1846570T6 (COLNNOT09), 2843910H1 (DRGLNOT01)

TABLE 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
1	300	S3 S15 S19 S20 S24 T98 S125 S231 T238 S257 S282 S12 S41 S70 T120 T143 S146 T242	N85 N88 N96	Protein kinase motifs: G161-F256 catalytic tk domain IX: V180-E202	Protein kinase	BLAST PFAM PRINTS
2	147	S85 T38 S90		Calcium-binding repeat motifs: G28-L115	PKC-potentiated inhibitory protein of PP1 (CPI17)	BLAST PRINTS BLOCKS
3	431	T178 S282 T25 S34 S75 S106 S194 S198 T208 T264 S299 S303 S304 S308 T328 S345 S388 T46 S137 S260	N44 N242	PTK signatures: A18-Y283 ATP-binding site: I30-K53, E127-G164 Y196-H219 PK catalytic subdomains: M99-E112, Y134-L152 G181-I191, Y243-A265	Ste20-like protein kinase	BLOCKS PRINTS PROFILESCAN BLAST
4	218	S108 S68 S90 T133 T170 S172 T34 T123 T207		Phosphofructokinase domains: I47, V177-Q195 L148-Y164		PRINTS

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
5	474	S14 S89 S98 S132 S472 T22 S26 S62 S66 T204 T320 T345 T359 S427 S443 S94 S128 T211 T336 S443 Y155		Protein kinase family signature: Y144-F425	serine/threonine protein kinase	MOTIFS PFAM BLOCKS PRINTS ProfileScan BLAST
6	540	S102 S183 S267 T296 T301 S442 S34 S58 S180 S207 S224 T360 S374 S401 S428 S478 T484 Y23	N100 N391 N457 N537	Protein kinase family signature: L18-L287	serine/threonine protein kinase	MOTIFS PFAM BLOCKS PRINTS PROFILESCAN BLAST
7	454	S57 S69 S130 T203 T212 S338 S420 S91 T101 T220 S271 S295 T315 S359 S381 Y197	N55 N140 N218 N403 N437 N441	SH2 domain: W63-Y138, W354-Y428 PI 3 kinase P85 regulator: K153-G176, A216-N257, R287-N332	phosphatidyl-inositol 3-kinase	PFAM BLOCKS PRINTS BLAST
8	502	S246 T498 T21 S65 S76 T193 T203 S275 S312 S355 T484 S106 T222 S323 T498 Y347	N302 N414	Signal petide: M1-T21 SH2 domain: V70-E80 ER targeting signal: K499-L502	tyrosine kinase	SigPept BLOCKS MOTIFS BLAST

TABLE 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
9	281	T66 T140 T141 T182 S210	N117 N139	Signal peptide: M1-I76	calcium/calmodulin-dependent protein kinase	PFAM BLAST
10	510	T297 S323 S358 S51 T312 S323 T325 S329 T377 T390 T483 S24 S152 T201 S210 S247 T292 T406 T407	N185 N349 N381 N405	Protein kinase family signature: R52-V261	Serine/threonine protein kinase	PFAM BLOCKS PRINTS MOTIFS BLAST
11	248	S5 S20 S36 T210 T245	N208	Tyrosine specific phosphatase active site: F166-A220 Dual specificity phosphatase: H95-R240	Tyrosine phosphatase or Dual specificity phosphatase	BLAST, MOTIFS BLOCKS, PRINTS PROFILESCAN PFAM

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
12	810	S62 S290 T429 S758 T17 T104 S108 T216 S279 T316 S330 T360 S386 T405 S425 S465 T473 S497 T547 T561 T715 S733 S738 S768 S196 S222 S229 S267 T281 T321 T347 S370 T400 T512 S534 T609 S617 S663 S751 T754 T762 Y67	N33		Protein kinase	BLAST, MOTIFS
13	549	S6 T502 T21 T116 S125 S320 T417 S46 S87 T240 S390 S397 S405 S430 S497	N238	ATP/GTP-binding site (p-loop): G58-T65 Protein kinase signature: I176-K199 I292-L304 Y347-L370 F456-L483	Dual specificity tyrosine/serine protein kinase	BLAST, MOTIFS BLOCKS, PRINTS PFAM
14	416	S312 T20 T97 S104 S183 T185 T211 T274 S381 S411 S72 S79 S140 S318 Y53		SH3 domain: A366-D384 N402-E414	PEST phosphatase interacting protein	BLAST, MOTIFS BLOCKS, PRINTS PFAM

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
15	425	T34 S233 S234 S25 S107 T144 T198 T250 S251 S258 S282 S300 S324 S345 T390 T51 T133 S365 S383 Y71	N23 N176 N362		SH3 binding protein	BLAST, MOTIFS
16	1135	S77 T187 S259 S554 S815 S9 S17 T59 S112 T124 T222 S264 T319 S324 S326 S550 T572 S625 S681 S682 T688 T689 S706 S720 T931 S958 S978 S999 S255 T309 T351 T543 S550 S624 S632 S726 T811 S898 S1012 S1113 Y321 Y323 Y467	N33 N570 N718 N1067	Protein kinase signature: V31-K54 V149-L161 W129-V182 Tyrosine kinase catalytic site: G190-I200 S214-M236 NIK1-like kinase domain: Y836-R1115	NIK kinase	BLAST, MOTIFS PROFILESCAN BLOCKS, PRINTS PFAM
17	228	T163 S60 T78 T68 S88 S147	N19 N100 N114		Interferon-induced PK regulator (P52rIPK)	BLAST

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
18	503	S51 T262 T36 S79 T94 S109 T361 T362 T403 S472 T47 S334 S343 Y17	N313 N333 N360	Protein kinase signature: I20-K43 V132-L144 V195-E217 Protein kinase domain: Y14-V272	calcium /calmodulin-dependent protein kinase II, beta 3 isoform	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILESCAN
19	433	S12 S77 S124 S131 S255 S290 T327 S365 S402 T70 Y88			Choline kinase isolog 384D8_3	BLAST, MOTIFS
20	527	S417 S154 S199 T367 S453 T120 S178 S413 T447 S473	N470	Protein kinase signature: I144-K167 I260-V172 ATP-binding site: Q247-G284 Y318-F341 Protein kinase domain: I138-L427	MAP-related protein kinase	BLAST, BLOCKS MOTIFS, PFAM, PROFILESCAN

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
21	322	S19 S122 T198 T200 T236 S251 T260 S264 T301 S14 S52 T181 T225	N196 N249	Protein kinase signature: L163-I175 ATP-binding site: M150-V187 I224-H247 Protein kinase domain: S32-E316	Protein tyrosine kinase	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILESCAN
22	802	S70 T87 S750 T14 T98 S144 T150 S230 S263 T353 T465 T470 S517 S633 T751 S758 T27 T74 T100 T207 S268 S368 S458	N36 N655	Protein kinase signature: L55-K81, L432-K455 ATP-binding site: E160-G197, H232-F255 PTK catalytic domain: H534-F552, C603-H625 Protein kinase domains: F49-F318, L427-L687 Protein kinase C domain: Q319-I382	Ribosomal S6 protein kinase	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILESCAN
23	641	S51 T262 S398 S436 S479 T36 S79 T94 S109 T375 T376 T541 S610 T47 S315 S333 S342 S393 S422 S431 S465 S474 S508 Y17	N313 N332 N374	Protein kinase signature: I20-K43 V132-L144 ATP-binding site: Q119-A156 Y191-F214 Protein kinase domain: Y14-V272	Ca2+ /calmodulin dependent protein kinase	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILESCAN

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods

24	588	S106 T155 S359 T388 T456 T531 T4, S58 S108 T126 S132 T279 S350 S436 S469 S508 S537 Y32	N63 N130 N574	Protein kinase catalytic domain: Y209-S445, F495-I522 ATP-binding site: I215-K238 STK core catalytic motif: I331-L343	Protein kinase Dyrk2	MOTIFS PFAM BLOCKS PRINTS BLAST
25	389	S31 T301 S56 S96 S134 T149 S186 S201 S283 S358 S375 Y148 Y165	N257 N343 N364	Protein kinase catalytic domain: E73-I311 STK core catalytic motif: I172-Y184 PTK core domain: D152-D208	CaM-like protein kinase	BLAST PFAM MOTIFS BLOCKS PRINTS PROFILESCAN
26	343	S68 S81 S137 S184 T219 S276 S297 T29 T125 Y86 Y211	N332	EF hand calcium-binding signature: D176-L188	protein phosphatase 2A (PR72)	BLAST MOTIFS BLOCKS
27	184	S36 T105 S40 S70 T117 Y50	N62	Tyrosine phosphatase active site domain: L63-V118	MAP kinase phosphatase (X17C)	BLAST PROFILESCAN BLOCKS PRINTS MOTIFS

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
28	118	S34 S84	N43	Signal peptide: M1-A27 PDZ domain: H8-S73	tyrosine phosphatase	SPScan PFAM BLAST
29	356	S9 S94 T209 T220 S259 S337 S5 S26 S75 S121 T154 S282 S332 S339 Y15 Y84	N333	tyrosine-specific protein phosphatase active site: I108-K164	tyrosine phosphatase (myotubularin)	PROFILESCAN MOTIFS BLOCKS PRINTS BLAST
30	453	S38 S73 S119 S131 S193 S200 T236 S293 S341 T379 T124 S173 T214 S252 T256 S282 S302 S313 S391 S397	N43 N67 N357	protein phosphatase 2A p55 subunit: P10-K451	protein phosphatase 2A p55 regulatory subunit, alpha isoform	PFAM MOTIFS BLOCKS PRINTS BLAST

TABLE 3

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
31	Hematopoietic/Immune (0.333) Reproductive (0.333)	Cell proliferation (0.500) Inflammation (0.333)	PBLUESCRIPT
32	Nervous (0.216) Reproductive(0.235) Cardiovascular (0.118)	Cell proliferation (0.530) Inflammation (0.352)	pINCY
33	Reproductive (0.293) Gastrointestinal (0.192)	Cell proliferation (0.641) Inflammation (0.335)	pINCY
34	Reproductive (0.284) Nervous (0.210) Cardiovascular (0.1213)	Cell proliferation (0.729) Inflammation (0.272)	pINCY
35	Nervous (0.529) Developmental (0.118) Gastrointestinal (0.118)	Cell proliferation (0.588) Neurological (0.118) Inflammation (0.118)	pINCY
36	Hematopoietic/Immune (0.268) Reproductive (0.244) Nervous (0.122)	Inflammation (0.488) Cell Proliferative (0.415)	PBLUESCRIPT
37	Reproductive (0.400) Hematopoietic/Immune (0.160) Nervous (0.160)	Cell proliferation (0.600) Inflammation (0.320)	pINCY
38	Cardiovascular (0.312) Reproductive (0.312) Developmental (0.188)	Cell proliferation (0.938) Inflammation (0.125)	pINCY
39	Nervous (0.400) Gastrointestinal (0.267) Developmental (0.133)	Cell proliferation (0.733) Neurological (0.133) Inflammation (0.133)	pINCY
40	Gastrointestinal (0.267) Nervous (0.233) Reproductive (0.167)	Inflammation (0.533) Cell proliferation (0.534)	pSPORT1

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
41	Musculoskeletal (0.500) Developmental (0.167) Gastrointestinal (0.167)	Cancer (0.834) Inflammation (0.167)	PBLUESCRIPT
42	Reproductive (0.240) Nervous (0.151) Gastrointestinal (0.135)	Cell proliferation (0.536) Inflammation (0.417)	pSPORT1
43	Hematopoietic/Immune (0.278) Nervous (0.222) Dermatologic (0.111)	Cell proliferation (0.444) Inflammation (0.389)	pINCY
44	Hematopoietic/Immune (0.500) Gastrointestinal (0.125) Nervous (0.125)	Inflammation (0.500) Cell proliferative (0.500)	PBLUESCRIPT
45	Nervous (0.220) Reproductive (0.213) Hematopoietic/Immune (0.140)	Cell proliferation (0.573) Inflammation (0.380)	pSPORT1
46	Hematopoietic/Immune (0.190) Gastrointestinal (0.165) Nervous (0.139)	Cell proliferation (0.582) Inflammation (0.354)	pSPORT1

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
47	Nervous (0.333) Reproductive (0.333) Hematopoietic/Immune (0.111)	Cancer (0.444) Inflammation (0.222) Neurological (0.111)	PBLUESCRIPT
48	Nervous (0.724) Cardiovascular (0.103)	Inflammation (0.276) Cancer (0.241) Neurological (0.172)	pINCY
49	Reproductive (0.235) Hematopoietic/Immune (0.188) Gastrointestinal (0.129)	Cancer (0.447) Inflammation (0.282) Fetal (0.153)	pINCY
50	Nervous (0.368) Developmental (0.158) Gastrointestinal (0.105)	Cancer (0.368) Fetal (0.211) Inflammation (0.105)	pSPORT1
51	Cardiovascular (0.312) Hematopoietic/Immune (0.312) Reproductive (0.158)	Fetal (0.688) Cancer (0.421) Inflammation (0.125)	pINCY
52	Reproductive (0.412) Nervous (0.235) Developmental (0.118)	Cancer (0.471) Fetal (0.235) Inflammation (0.235)	pINCY
53	Nervous (0.714) Cardiovascular (0.107)	Cancer (0.250) Inflammation (0.250) Neurological (0.179)	pINCY

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	PBLUESCRIPT
54	Reproductive (0.533) Nervous (0.133)	Cell proliferation (0.601) Inflammation (0.270)	PBLUESCRIPT
55	Hematopoietic/Immune (0.278) Nervous (0.222) Reproductive (0.154)	Cell proliferation (0.388) Inflammation (0.333) Neurological (0.111)	PBLUESCRIPT
56	Hematopoietic/Immune (0.211) Cardiovascular (0.193) Nervous (0.175)	Cell proliferation (0.474) Inflammation (0.491)	PBLUESCRIPT
57	Reproductive (0.286) Cardiovascular (0.229) Musculoskeletal (0.143)	Cell proliferation (0.715) Inflammation (0.200)	pINCY
58	Nervous (0.667) Reproductive (0.333)	Cancer (1.000)	pSPORT1
59	Reproductive (0.357) Cardiovascular (0.179) Nervous (0.125)	Cancer and Cell proliferation (0.642) Inflammation and Immune Response (0.232)	pSPORT1
60	Nervous (0.228) Reproductive (0.175) Cardiovascular (0.158) Hematopoietic/Immune (0.158)	Cancer (0.368) Inflammation and Immune Response (0.263) Fetal (0.211)	pINCY

TABLE 4

Polynucleotide SEQ ID NO:	Library	Library Comment
31	BMARNOT02	Library was constructed using RNA isolated from the bone marrow of 24 male and female Caucasian donors, 16 to 70 years old.
32	SININOT01	Library was constructed using RNA isolated from ileum tissue removed from the small intestine of a 4-year-old Caucasian female, who died from a closed head injury. Patient history included jaundice as a baby. Previous surgeries included a double hernia repair
33	SPLNFET02	Library was constructed using RNA isolated from spleen tissue removed from a Caucasian male fetus, who died at 23 weeks' gestation from premature birth. Family history included diabetes.
34	OVARTUT02	Library was constructed using RNA isolated from ovarian tumor tissue removed from a 51-year-old Caucasian female during an exploratory laparotomy, total abdominal hysterectomy, salpingo-oophorectomy, and an incidental appendectomy. Pathology indicated mucinous cystadenoma presenting as a multiloculated neoplasm involving the entire left ovary. The right ovary contained a follicular cyst and a hemorrhagic corpus luteum. The uterus showed proliferative endometrium and a single intramural leiomyoma. The peritoneal biopsy indicated benign glandular inclusions consistent with endosalpingiosis. The patient presented with abnormal weight gain and ascites. Patient history included depressive disorder, joint pain, allergies, alcohol use, and a normal delivery. Family history included atherosclerotic coronary artery disease, benign hypertension, breast cancer and uterine cancer.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
35	PANCTUT01	library was constructed using RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, and benign neoplasm in the large bowel. Previous surgeries included a total splenectomy, cholecystectomy, and abdominal hysterectomy. Family history included cardiovascular disease, type II diabetes, and stomach cancer.
36	SMCBUNT01	library was constructed using RNA isolated from bronchial smooth muscle cell tissue removed from a 21-year-old Caucasian male.
37	UTRSTUT05	Library was constructed using RNA isolated from uterine tumor tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with dilation and curettage. Pathology indicated uterine leiomyoma. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Patient history included a ventral hernia and a benign ovarian neoplasm.
38	UTRSTUT04	library was constructed using RNA isolated from uterine tumor tissue removed from a 34-year-old Caucasian female during a hysteroscopy and an exploratory laparotomy with dilation and curettage. Pathology indicated an endometrial polyp, subserosal leiomyoma, and fragments of leiomyoma. Family history included hyperlipidemia, depressive disorder, benign hypertension, cerebrovascular disease, arteriosclerotic cardiovascular disease, and type II diabetes.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
39	SMCBUNT01	library was constructed using RNA isolated from bronchial smooth muscle cell tissue removed from a 21-year-old Caucasian male.
40	ADRENOT03	library was constructed using RNA isolated from the adrenal tissue of a 17-year-old Caucasian male, who died from cerebral anoxia.
41	TESTNOT04	library was constructed using RNA isolated from testicular tissue removed from a 37-year-old Caucasian male who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
42	BRSTTUT01	library was constructed using RNA isolated from breast tumor tissue removed from a 55-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated invasive grade 4 mammary adenocarcinoma of mixed lobular and ductal type, extensively involving the left breast. The tumor was identified in the deep dermis near the lactiferous ducts with extracapsular extension. Seven mid and low and five high axillary lymph nodes were positive for tumor. Proliferative fibrocysytic changes were characterized by apocrine metaplasia, sclerosing adenosis, cyst formation, and ductal hyperplasia without atypia. Patient history included atrial tachycardia, blood in the stool, and a benign breast neoplasm. Family history included benign hypertension, atherosclerotic coronary artery disease, cerebrovascular disease, and depressive disorder.
43	LUNGNOT10	library was constructed using RNA isolated from the lung tissue of a Caucasian male fetus who died at 23 weeks' gestation.
44	UCMCL5T01	library was constructed using RNA isolated from mononuclear cells obtained from the umbilical cord blood of 12 individuals. The cells were cultured for 12 days with IL-5 before RNA was isolated from the pooled lysates.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
45	BRSTTUT03	library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes.
46	BRSTNOT05	library was constructed using RNA isolated from breast tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated multicentric invasive grade 4 lobular carcinoma. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular and cardiovascular disease, breast and prostate cancer, and type I diabetes.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
47	SPLNNOT02	The library was constructed using RNA isolated from the spleen tissue of a 29-year-old Caucasian male, who died from head trauma. Serologies were positive for cytomegalovirus (CMV). Patient history included alcohol, marijuana, and tobacco use.
48	BRAITUT08	The library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 47-year-old Caucasian male during excision of cerebral meningeal tissue. Pathology indicated grade 4 fibrillary astrocytoma with focal tumoral radionecrosis. Patient history included cerebrovascular disease, deficiency anemia, hyperlipidemia, epilepsy, and tobacco use. Family history included cerebrovascular disease and a malignant prostate neoplasm.
49	PANCTUT01	The library was constructed using RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, benign neoplasm in the large bowel, and a cataract. Previous surgeries included a total splenectomy, cholecystectomy, and abdominal hysterectomy. Family history included cardiovascular disease, type II diabetes, and stomach cancer.
50	BRAITUT02	The library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
51	THP1NOT03	The library was constructed using RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
52	BRSTNOT12	The library was constructed using RNA isolated from diseased breast tissue removed from a 32-year-old Caucasian female during a bilateral reduction mammoplasty. Pathology indicated nonproliferative fibrocystic disease. Family history included cardiovascular disease.
53	MUSCNOT07	The library was constructed using RNA isolated from muscle tissue removed from the forearm of a 38-year-old Caucasian female during a soft tissue excision. Pathology for the associated tumor tissue indicated intramuscular hemangioma. Family history included breast cancer, benign hypertension, cerebrovascular disease, colon cancer, and type II diabetes.
54	HUVESTB01	Library was constructed using RNA isolated from shear-stressed HUV-EC-C (ATCC CRL 1730) cells. HUV-EC-C is an endothelial cell line derived from the vein of a normal human umbilical cord (ref:PNAS 81:6413).
55	THYMNOT02	ibrary was constructed using polyA RNA isolated from thymus tissue removed from a 3-year-old Caucasian male, who died from drowning.
56	CARDNOT01	Library was constructed using RNA isolated from the cardiac muscle of a 65-year-old Caucasian male, who died from a self-inflicted gunshot wound.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
57	UTRSNOT12	Library was constructed using RNA isolated from uterine myometrial tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with a dilatation and curettage. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Pathology for the associated tumor tissue indicated uterine leiomyoma. The patient presented with an unspecified menstrual disorder. Patient history included ventral hernia, normal delivery, a benign ovarian neoplasm, and tobacco abuse. Previous surgeries included a bilateral destruction of fallopian tubes, removal of a solitary ovary, and an exploratory laparotomy.
58	PGANNOT01	Library was constructed using RNA isolated from paraganglionic tumor tissue removed from the intra-abdominal region of a 46-year-old Caucasian male during exploratory laparotomy. Pathology indicated a benign paraganglioma and association with a grade 2 renal cell carcinoma, clear cell type.
59	BEPINOT01	Library was constructed using RNA isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male.
60	DRGLNOT01	Library was constructed using RNA isolated from dorsal root ganglion tissue removed from the low thoracic/high lumbar region of a 32-year- old Caucasian male who died from acute pulmonary edema and bronchopneumonia, bilateral pleural and pericardial effusions, and malignant lymphoma (natural killer cell type). Patient history included probable cytomegalovirus infection, hepatic congestion and steatosis, splenomegaly, hemorrhagic cystitis, thyroid hemorrhage, and Bell's palsy.